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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,518	06/20/2003	Choong-Chin Liew	4231/2055	8219

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
12/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/601,518	**Applicant(s)** LIEW, CHOONG-CHIN	
	Examiner Juliet C. Switzer	**Art Unit** 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 December 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *03 December 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *17,19-21,23,24,28,29,31,33,34,38,41,43,49,56 and 59-63*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Juliet C Switzer/
Primary Examiner, Art Unit 1634

Continuation of 3. NOTE: The new claims include claims 65 and 67 which are much broader than previously filed claims since these claims merely comprise that the RNA is isolated from samples of "whole blood," which could include any isolation method of RNA from "whole blood" and is not limited only to methods in which the blood samples have not been fractionated into cell types. Thus, further search and consideration would be required, and the amendments will not be entered.

Continuation of 11. does NOT place the application in condition for allowance because:

Applicant argues that Sharma et al. fail to teach a critical element of a method for enabling isolation of RNA from whole blood, namely adding a ribonuclease inhibitor to blood samples during the freezing, thawing, and initial centrifugation steps. Applicant argues that Kephart exemplifies that without such addition, widespread degradation of RNA would occur. Applicant argues that because Sharma does not teach the addition of this reagent prior to the freeze/thaw/centrifugation cycle, the ordinarily skilled artisan would not consider the combined teachings of Sharma and any other reference to be enabling, an further would not have been motivated to combine the teachings of Sharma with any other reference because the Sharma reference lacks credibility because they did not teach the addition of this reagent prior to the freeze/thaw/centrifugation cycle.

It is noted, as applicant points out, that Sharma expressly teaches the addition of ribonuclease inhibitors after thawing and centrifugation. This is distinguished from the Kephart control where no ribonuclease inhibitor is added, ever, in the process. So, while it is reasonable to conclude that Kephart shows that adding ribonuclease inhibitor is essential in a process in which RNA is to be detected directly in blood (i.e. with no further purification), it is not fair to extend that finding to discredit the teachings of Sharma since in Sharma further purification occurs. There is no evidence present on the record that would demonstrate that the method practiced as Sharma presented it would not work, or even that it would not have been credible. Further, at the time the invention was made, there were methods for isolating and detecting mRNA which were known that utilized a freeze/thaw cycle followed by guanidine tyiocyanate isolation similar to that taught by Sharma had successfully been used (see for example Kurse et al., previously cited). Kruse et al. use tubes containing EDTA, a chemical which inhibits some, but not all RNAse activity, also exemplifying that this was a routinely used procedure at the time the invention was made. The fact that Sharma did not teach using EDTA tubes is not a showing of lack of credibility, it is to be construed for what it is: an inventor leaving out a step that is well known in the art.

Applicant notes that Sharma does give the details of solutions that are used in RNA isolation procedures, and since some details, but not a suggestion to immediately add an RNAse inhibitor the reference lacks credibility. This argument is not persuasive, because, as noted, this step is something that would have clearly been known to, and enabled by, the state of the art at the time Sharma was written. If, as applicant contends, anyone having ordinary skill in the art at the time the invention was made would have known this was a critical and essential step, then Sharma is not required to provide what was known to one of ordinary skill in the art.

Applicant appears suggests on the bottom of page 11 that Sharma teaches away from the claimed invention when they fail to positively recite adding an RNAse inhibitor. Here there is no teaching away identified, merely an absence of a particular detail of protocol, a detail that would have been WELL KNOWN (by applicant's own admission) to one having ordinary skill in the art.

Applicant criticizes the declaration filed in the application from which Sharma issued, since they are post-filing art and did not follow the guidance in the Sharma specification. Applicant states that the earlier declaration indicated delayed acquisition of credible skill in the art of whole blood isolation. However, applicant has not identified any process used in that declaration that was not routinely practiced at the time of the Sharma filing. Neither the instant application, nor the Sharma disclosure are directed at new techniques for the isolation and detection of mRNA in the blood- the methods employed in both applications were routine at the time the invention was made. What is disclosed in both applications are methods for finding markers in the blood.

The argument is not persuasive.

Applicant reiterates the arguments set forth prior to the final office action regarding the "prevailing paradigm" that biomarkers could only be found in blood samples that had been fractionated. The examiner maintains the position that this argument is not persuasive for the reasons of record, and again points to the prior art references which specifically demonstrate and suggest that markers could be identified in samples contain total blood RNA.

Applicant argues that there would have been no reasonable expectation of success to have provided the claimed methods of identifying two or more markers in whole blood that are useful for diagnosing a disease, since it had not been done before. However, as cited in the references, there was clear suggestion in the art that the method could be accomplished. There would have been high expectation of success given the secondary reference which identified multiple markers for disease in blood samples, albeit not whole blood samples. In the final rejection references were cited (Kruse, Chadderton, McFarlane et al.) which clearly suggest that there was an expectation of success for the use of whole blood samples, and total blood RNA in clinically relevant molecular biology applications. The argument is not persuasive. Applicant argues that these references establish methodologies but do not reduce the invention to practice. This is not evidence that there was no expectation of success.

The rejection is maintained.